Report of the Director

Report of the National Heart, Lung, and Blood Advisory Council

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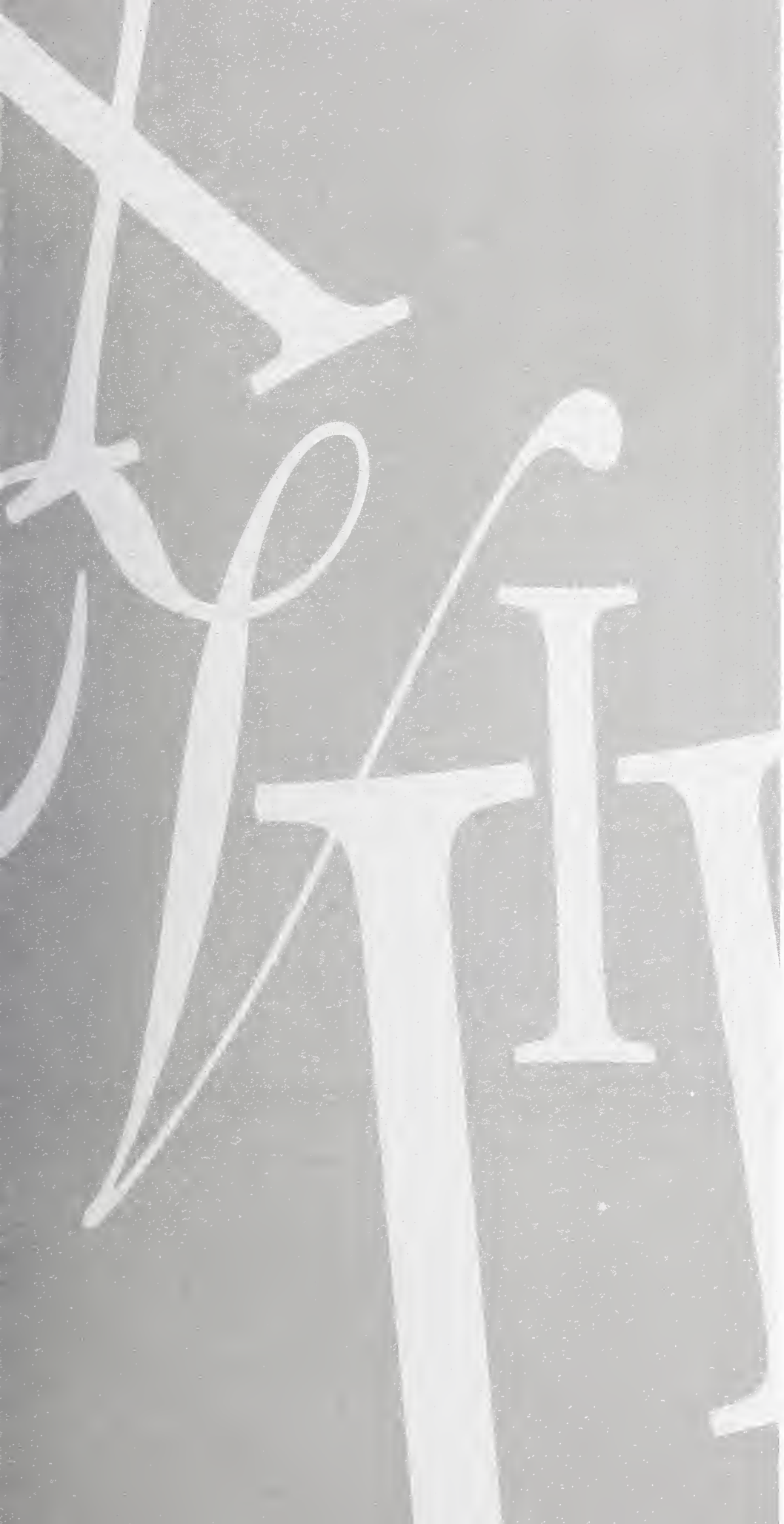

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Eighteenth Report of the Director

The National Heart, Lung, and Blood Institute (NHLBI) supports a comprehensive program of research related to diseases of the heart, blood vessels, lungs, and blood as well as the use and management of blood resources. Considerable progress has been made in understanding the fundamental nature of health and sickness and in uncovering new strategies for diagnosis, treatment, and prevention. Nonetheless, diseases under the Institute's mandate continue to have a major impact on society in terms of deaths, illness, hospitalization, lost productivity, and health care costs. To meet this continuing challenge, the NHLBI supports a comprehensive research program that includes basic and clinical investigations, population-based studies, and demonstration and education activities to move new research findings quickly into practice. A large variety of new research approaches—ranging from molecular biology to behavioral science—are now available, and the advances highlighted below attest to the NHLBI's recent successes and future plans utilizing these approaches.

Progress and Opportunities

Mild Hypertension

The Treatment of Mild Hypertension Study provides a scientific basis for recommendations concerning management of patients with mildly elevated blood pressure. The study found that, although lifestyle changes (weight reduction, decreased sodium intake, and increased physical activity) significantly lowered blood pressure, addition of drug treatment reduced it further and was associated with lower rates of heart enlargement and major cardiovascular illness, as well as with improvement in patients' health quality of life. These outcomes were observed regardless of the type of antihypertensive drug used. Recently a new clinical trial was initiated to determine whether treatment of hypertension with newer, more expensive drugs is more effective in preventing heart attacks and deaths than the less expensive diuretic drugs currently in use. The data will have important implications for more cost-effective management of hypertension.

Hypertrophic Cardiomyopathy (HCM)

HCM, a thickening of the heart muscle, is the most common inherited heart muscle disease and leading cause of sudden cardiac death in otherwise healthy young people. Recently, NHLBI intramural investigators identified a variety of genetic mutations in the heavy chain of ß-myosin, a muscle component, in the hearts of HCM patients. For example, two mutations have been identified that seldom result in disease and have a favorable prognosis, and a third mutation has been found to cause disease in 100 percent of affected persons and to confer a high risk of sudden death. The availability of these molecular markers has made it possible to perform presymptomatic diagnosis of HCM in children. Knowledge of the genetic defect involved in this disorder also provides an important basis for improved treatment tailored to individual patients.

Congenital Heart Disease

Recent advances in molecular biology have shown that many forms of congenital heart disease, a group of malformations of the heart that affect about 30,000 newborns in the United States (U.S.) each year, can be attributed to genetic defects. In one study in dogs, investigators found that many types of human "blue baby" malformations result from a single chromosomal mutation. Other research has identified a gene mutation responsible for coarctation of the aorta, a common abnormality that causes heart failure and premature death if not corrected surgically. Finally, the gene responsible for supravalvular aortic stenosis, which can produce heart failure and other heart problems in infants and children, has been identified. Extension of this research is expected to provide new approaches for improved prenatal diagnosis and treatment, genetic counseling for disease prevention and, ultimately, gene therapy for congenital heart disease.

Clinical Trials

Clinical trials assess the efficacy of therapeutic or preventive strategies in reducing illness or death; compare outcomes among persons of different gender, racial/ethnic group, or health status; and address such issues as health quality of life and cost-effectiveness. For example, results of a new clinical trial, Antiarrhythmics Versus Implantable Defibrillators (AVID), will determine whether patients resuscitated from life-threatening arrhythmias fare better with an implantable cardiac defibrillator (ICD) or with the drugs amiodarone or sotalol. This information will be valuable for management of patients with serious ventricular arrhythmias. Furthermore, by improving the ability to identify subgroups of patients likely to benefit from the ICD, it will facilitate appropriate use of this new procedure.

Cystic Fibrosis (CF)

Important new research advances demonstrate that gene therapy has the potential to correct the underlying defect in CF, the leading hereditary cause of death in children and young adults in the U.S. Several human gene therapy protocols are now under way. Success has been achieved in demonstrating expression of the normal CF gene and correction of the chloride transport defect characteristic of CF cells. These exciting studies will be expanded in the six gene therapy centers recently established by the NHLBI, where answers will be sought to many important questions that remain about the safety and efficacy of gene therapy for CF. Other innovative approaches to CF treatment include use of drugs to activate or increase expression of the mutant gene in patients and use of mucus-thinning agents to alleviate the symptoms of CF. These and other therapeutic avenues promise to improve the health quality of life and longevity of CF patients.

Gene Therapy for Acquired Diseases

Although the objective of gene therapy has been to obtain long-term expression of normal proteins that are deficient or defective in inherited diseases, a new direction is its use to accomplish short-term or transient increases in protein expression for acquired diseases. To this end, a number of physiologically important genes have been successfully introduced into lung cells in culture and animal lungs in vivo, and have been expressed well for about 7 days. This approach has considerable potential for treatment of acute lung injury, where even short-term increases in protective antioxidants or anti-inflammatory agents could be helpful for lung repair.

Transfusion Medicine

Despite advances in transplantation and transfusion science, a major complication that remains is rejection of the graft or transfusion by the recipient's immune system. A logical approach to overcome this problem would be to induce specific suppression (i.e., tolerance for the foreign transplantation antigens involved) without affecting host immune response to infections. During the past year, promising preliminary

results were obtained in an animal model. Animals pretreated with a soluble form of a transplantation antigen were later unable to produce antibodies to the normal, cell-bound form of that antigen, although their general immune responses remained intact. If this technique proves successful in humans, it suggests the exciting possibility of converting incompatible donors into compatible ones and, thereby, increasing the number of available platelet and bone marrow matches without increasing the size of the donor pool.

Hemophilia

Hemophilia A is a hereditary bleeding disorder that results from a deficiency in factor VIII, a blood coagulation protein. Affected individuals are subject to spontaneous bleeding episodes and risk crippling joint injuries or life-threatening hemorrhage. The seriousness of the disorder is related to the level of factor VIII activity and is classified as severe, moderate, or mild. Sequencing of the factor VIII gene and subsequent studies identified mutations in most of the mild-to-moderate patients and about one-half of the severe patients, but the genetic defect in the remainder of patients was unidentifiable. Recently, researchers found evidence that such cases may be caused by an inversion of the factor VIII gene. The availability of a newly developed assay, based upon this information, is expected to improve genetic counseling and enable prenatal diagnosis in families affected by hemophilia A.

Thrombolytic Therapy

New drugs are now available that may allow thrombolysis (dissolution of blood clots) in blocked arteries without creating the problem of unwanted bleeding elsewhere in the body. Recently, molecular biology techniques were used to produce a mutant tissue-type plasminogen activator (tPA) that is inactive until it becomes attached to fibrin in the occlusive clot. It can then be cleaved into an active form. If detailed safety and efficacy studies confirm these findings and the drug becomes commercially available, it is expected to improve the quality of care for the nearly 200,000 patients who receive thrombolytic therapy each year. It may also permit extension of this lifesaving treatment to a broader range of heart attack patients.

Gene Therapy for Sickle Cell Disease (SCD)

The NHLBI has initiated a new research program to explore genetic therapy approaches for the cure of SCD, a worldwide health problem that affects 1 in 400 black newborns in the U.S. A number of recent advances have paved the way for rapid progress in this area. First, new methods allow accurate and efficient isolation of red blood cell precursors, which can be manipulated outside the body and then reintroduced into the patient. Second, both viral and nonviral vectors offer promise of efficient means of introducing normal hemoglobin genes into these cells. Finally, new understanding of hemoglobin gene regulation is expected to enable expression of the newly introduced genes in red cell precursors. A gene therapy cure would significantly improve the health of black Americans and greatly reduce the cost of care for SCD, which exceeds $700 million annually.

Sleep Disorders

The magnitude and prevalence of sleep disorders have only recently been recognized. The most common condition, sleep apnea (cessation of breathing during sleep), affects about 20 million Americans and is associated with cardiopulmonary disorders, mental impairment, and injury from accidents. To address the many health problems related to sleep disorders, the National Institutes of Health Revitalization Act of 1993 established the National Center on Sleep Disorders Research within the NHLBI. The Center, whose programs will be coordinated with similar activities at the NIH and other federal components, will conduct and support research, research training, and health information dissemination related to this major public health problem.

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Eighteenth Report of the National Heart, Lung, and Blood Advisory Council

The decade of the 1990s has brought both unprecedented scientific opportunities and enormous fiscal and administrative challenges to the National Heart, Lung, and Blood Institute (NHLBI). The many, sometimes conflicting, demands of the research enterprise—basic versus applied research, large versus small grants, emerging versus traditional disciplines, "high-risk" versus conventional approaches—all have been the subject of lively and thoughtful discussion by the National Heart, Lung, and Blood Advisory Council. The recommendations that ensued from these debates have been guided by the Council's firm commitment to a balanced program that strives to maintain the momentum and stability of the past while capitalizing fully on the scientific promise of the future.

This report highlights some of the important topics considered by the Council at recent meetings. They illustrate the excitement and potential of new research frontiers, the difficulties of allocating scarce resources in an optimal fashion, and some innovative public health approaches that are a source of distinction and pride for the Institute and its Council.

Molecular Genetics: A New Frontier

Ever since the first human gene therapy experiment was conducted in late 1989, the NHLBI has been at the forefront of research in the new discipline of molecular biology. The emerging capability to identify and modify genes that cause disease is expected to have far-reaching effects. These include improved methods for presymptomatic diagnosis, carrier detection, primary prevention, and cure of diseases that affect the cardiovascular, pulmonary, and hematologic systems.

Considerable progress is already being made with respect to diseases that are caused by a single defective gene, such as cystic fibrosis, hemophilia, and sickle cell anemia. Indeed, we have every reason to anticipate that cures through genetic therapy are within reach. To guide and advance its research efforts in this area, the Institute convened a Working Group on Gene Therapy Approaches and Resources for Heart, Lung, and Blood Diseases to examine ways in which existing knowledge could be used to devise effective methods of genetic therapy for these diseases. The Working Group's recommendations have already led to development of three Institute-initiated programs to move this work forward to a successful conclusion: "Gene Therapy Approaches for Cystic Fibrosis and Other Heart, Lung, and Blood Diseases"; "Gene Therapy for Sickle Cell Disease"; and "Gene Therapy for Hemophilias A and B." These targeted efforts are expected to revolutionize our mastery over diseases that have plagued generations of families.

Even more exciting is the potential application of molecular genetic approaches to multifactorial diseases, such as high blood pressure and asthma, that affect millions of Americans. These diseases represent a new frontier because they do not follow the classical laws of genetics and because they involve special medical and societal

challenges that make progress difficult. To identify scientific priorities in this area, the Institute formed an Expert Panel on Genetic Strategies for Heart, Lung, and Blood Diseases, which recently produced a master plan that describes major research opportunities and operational strategies for their implementation. Several new research initiatives have already been developed pursuant to this plan, including a shared support facility for mammalian genotyping and a collaborative program to delineate the major genetic determinants of high blood pressure.

Although only molecular biology is highlighted in this report, many other scientific opportunities of equal excitement and importance have been the subject of Council discussion and action recently. The Council has enthusiastically endorsed a number of new research directions, recognizing their potential for unprecedented strides toward improving the public health.

Funding Mechanisms

The rapid emergence of new scientific opportunities, coupled with the continuing promise of more traditional lines of inquiry, underscores the importance of managing the Institute's resources so that an appropriate balance between stability and flexibility is achieved. The NHLBI has long been guided by the philosophy that it is necessary and desirable to use a variety of funding mechanisms, ranging from investigator-initiated regular research grants to Institute-initiated contract solicitations, to fulfill its mission. As appropriations for the Institute have leveled off in recent years, competition for funds has increased among recipients of various types of support. The share of resources devoted to large grants—Specialized Centers of Research (SCORs) and program projects—has been a particular focus of concern. The Council believes that the new policies it has endorsed with respect to such grants, described below, take advantage of the best that these funding mechanisms have to offer and make optimal use of available resources.

Specialized Centers of Research

Since 1971, the NHLBI has supported SCORs to advance basic knowledge and develop techniques and methods of clinical management and prevention in selected areas of heart, blood vessel, lung, and blood research. These centers provide a unique opportunity for basic and clinical scientists from a variety of disciplines to collaborate on research in a particular disease area. Because the Institute has a mandate to focus on specific diseases, a large measure of its success comes from the rapid translation of research findings to the bedside. The SCOR program is critical to that effort because it is uniquely and often exclusively the Institute's avenue for clinical research on a given disease. The program ensures that advances in basic sciences are translated rapidly into clinical application and that clinical needs provide direction for fundamental investigations.

It is clear that the SCOR mechanism provides a valuable complement to other components of the NHLBI research portfolio. However, concerns have been raised that, over the years, the SCOR programs may have lost some of the concept of "specialness" that originally justified their establishment as Institute-initiated programs. During fiscal year 1992, the Institute supported SCORs in 13 scientific areas; while several were in only their initial or second 5-year period, others had endured as long as 22 years through five different solicitations. Whether all these scientific areas continued to require special stimulation by this mechanism was called into question.

The Council devoted considerable attention to this matter at its September 1992 meeting and unanimously expressed its opinion that the concept of "sunset" should be incorporated into the SCOR program. A motion was passed that any given SCOR program be limited to 10 years of support, and that SCOR programs already exceeding that duration be terminated at the end of the next 5-year renewal period. Exceptions to

this policy may be made only if a thorough evaluation of research needs and opportunities uncovers extraordinarily compelling reasons to continue a specific SCOR program. Indeed, the goal of this evaluation is not to focus on the accomplishments of a given SCOR program but, rather, to identify timely and needy scientific areas that stand to benefit most from this specialized research approach. The Council expects that this "sunset" provision will open the door on a host of new research opportunities and enable the Institute to direct its limited resources where the payoff is likely to be greatest.

Program Project Grants

Because of the Institute's broad mission with respect to fundamental and clinical investigations, program project grants constitute an important and visible part of its research portfolio. These grants are a vital catalyst for innovative, multidisciplinary research programs that offer unique opportunities for scientific discovery. Nonetheless, the high costs associated with program project grants—in terms of both the dollars awarded and the administrative burden to the Institute—have prompted much discussion.

A significant area of controversy about program project grants is the extent to which they consume resources that might otherwise be allocated to the remainder of the research project grant (RPG) budget. Although program project grants, on average, have accounted for about 19 percent of Institute expenditures on RPGs over the past decade, their annual share of competing awards has oscillated between 15 and 25 percent, causing concomitant fluctuations in the Institute's ability to fund regular research grants. To remedy this problem, the Institute, with the endorsement of Council, has opted to set aside, on an annual basis, a specific portion of its funds for support of competing and noncompeting program project grants. This amount is not a "floor" but a "ceiling"; thus, its full utilization is contingent on receipt of sufficient numbers of meritorious applications. By allocating a specific percentage of its RPG budget for program project grants, the Institute hopes to enhance the stability, predictability, and balance of its funding mechanisms.

The Institute also has made a number of changes in review procedures for program project grants, both to reduce the administrative burden and to facilitate selection of the most highly meritorious applications for funding. On-site review visits have been eliminated; instead, "reverse" site visits are offered to applicants.* The Council expressed a number of concerns about this change, but recognized its necessity in the face of scarce resources. Further, the Institute has adopted a policy, to begin in fiscal year 1995, that only one amended version of a given program project grant application will be accepted for consideration.

The respective roles and responsibilities of the reverse site-visit and parent peer review committees have also been modified. Under the new guidelines, reviewers participating in the reverse site visit continue to assign numerical priority scores based on scientific merit to each proposed subproject, but no longer vote an overall priority score for the program project application. A single parent review committee then is responsible for reviewing the reverse site visit report and its subproject priority scores and voting an overall priority score that reflects the synergy of the program as a whole, the scientific merit of its subprojects, the significance of the research, and other considerations that relate to the program's feasibility and potential. The Council believes that this new balance of responsibilities will facilitate thoughtful, critical review and thus enable the Institute to continue its tradition of supporting high-quality research through the program project grant mechanism.

*Note: Beginning with applications for funding in fiscal year 1996, the Institute eliminated all forms of site-visits as part of its standard review process for program project grants.

Prevention, Education, and Control Activities

A special attribute of both SCORs and program project grants is their ability to bridge the gap between fundamental research findings and health-care practices that are beneficial to the patient. However, these and other research efforts alone are not sufficient to achieve the public health objectives of the NHLBI. The Institute has long recognized that an important aspect of its mandate encompasses technology transfer through well-designed education and prevention programs for health-care professionals, patients, and the general public. Such efforts now assume greater importance than ever in light of this country's growing interest in approaching disease from the preventive, rather than the therapeutic, standpoint. For over 20 years, the Institute has been a leader in developing innovative and effective programs to disseminate information about major risk factors for cardiovascular diseases—high blood pressure, elevated serum cholesterol, and smoking—as well as programs to improve awareness and management of asthma and to facilitate appropriate maintenance and use of the Nation's blood supply. Several new directions merit special mention.

High Blood Pressure

The National High Blood Pressure Education Program (NHBPEP), established in 1972, has been a model for rapid and effective translation of research results to the community. Over the years, the NHBPEP has regularly examined the latest scientific developments and achieved consensus on those that are ready for transfer to health-care professionals and the public. The program has succeeded in increasing public awareness of high blood pressure and its risks, encouraging Americans to have their blood pressure checked, and stimulating adherence to treatment.

Despite the clear benefit of treating established hypertension, that approach alone will not entirely prevent the deleterious consequences of high blood pressure. Thus, the NHBPEP has embarked upon a new effort to prevent blood pressure elevations from developing. The recent Working Group Report on Primary Prevention of Hypertension identified two complementary disease prevention approaches—a population strategy and a strategy targeted to high-risk individuals. The program will encourage all Americans to reduce sodium intake, exercise more regularly, limit alcohol intake, and achieve and maintain a healthy weight in an effort to prevent the onset of hypertension. Primary prevention of hypertension provides unique opportunities for the Nation to reduce the costly cycle of managing hypertension and its complications.

Asthma

An increased emphasis on prevention is also apparent in the Institute's asthma-related technology transfer efforts. The former National Asthma Education Program has been renamed the National Asthma Education and Prevention Program to reflect this new orientation, which focuses on persons, especially minorities, with undiagnosed asthma. A mass media campaign has been implemented nationally to create greater awareness of asthma's warning signs and to encourage people who experience them to seek treatment. With appropriate treatment, asthma symptoms can be prevented and such individuals can lead normal, active lives. This broad-based approach is expected to bring modern asthma management to the many who would benefit from it and, thereby, reduce the human and monetary costs associated with this prevalent disease.

Blood Resources

In the area of blood resources, the Institute has devoted considerable effort to increasing recruitment of minority bone marrow donors.

Supplemental funds were awarded through the National Marrow Donor Program (NMDP) to develop and evaluate innovative approaches to address this important issue. During its initial year of operation, this program resulted in the addition of nearly 12 thousand new minority donors to the NMDP registry. These projects have provided valuable information about both effective and unsuccessful strategies for recruiting marrow donors from different ethnic and cultural groups. The results are expected to assist donor centers and community groups in attracting and retaining a diversity of donors of blood and blood products.

Conclusion

The Council commends the NHLBI director and staff for their enlightened leadership and dedicated service, and applauds the Institute's increasing efforts to enhance communication with the scientific community about policies that have an important impact on biomedical research support. The Institute's accomplishments are impressive, its approaches are sound, and its future is ripe with opportunity for continuing improvements in the public health of the United States.

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